DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

OCT 25 2001

Diane B. McColl
Hyman, Phelps and McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, DC 20005-5929

Re: GRAS Notice No. GRN 000078

Dear Ms. McColl:

The Food and Drug Administration (FDA) is responding to the notice, dated May 11, 2001, that you submitted on behalf of Arla Foods Ingredients amba (Arla) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on May 11, 2001 and designated it as GRAS Notice No. GRN 000078.

The subject of the notice is D-tagatose. The notice informs FDA of the view of Arla that D-tagatose is GRAS, through scientific procedures, for use as a bulk sweetener, humectant, texturizer, or stabilizer in a variety of foods as described in Table 1 (below) in accordance with current good manufacturing practice.

In the notice, Arla includes the report of a panel of individuals (Arla's GRAS panel) who evaluated the data and information that are the basis for Arla's GRAS determination. Arla considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Based on the data and information reviewed, Arla's GRAS panel concluded that D-tagatose that meets appropriate food grade specifications is GRAS, through scientific procedures, under the conditions of its intended use in accordance with the limitations of current good manufacturing practice.

D-tagatose is a stereoisomer of D-fructose, a common six carbon sugar. Specifically, D-tagatose and D-fructose are epimers, with their structures differing in the spatial configuration of the hydroxyl group at the chiral carbon atom at position 4 (C-4). The Chemical Abstracts Service Registry Number (CAS Reg. No.) of D-tagatose is 87-81-0. It has a sweetness of about 75-92 percent that of sucrose.

D-tagatose is manufactured from the enzymatic hydrolysis of food grade lactose, by immobilized *Aspergillus oryzae* lactase, to form D-galactose. D-galactose undergoes a chemical isomerization reaction induced by calcium hydroxide to form D-tagatose, which is purified by mineralization, ion exchange chromatography, and recrystallization. The notice provides specifications for food-grade D-tagatose, including a lead specification of not more than 0.5 mg/kg (i.e., parts per million (ppm)).

Based on the conditions of use described in Table 1, Arla informs FDA that the estimated daily intake (EDI) of D-tagatose would be 6.6 grams per person per day (g/p/d) at the mean and 14.9 g/p/d at the 90th percentile.[1]

Table 1
Conditions of Use Proposed by Arla

Food Category	Maximum Level of Use
Diet and/or sugar free carbonated beverages	1 percent
Sugarless and sugar free chewing gum	60 percent
Ready-to-drink teas presweetened with low calorie sweeteners	1 percent
Ready-to-eat cereals	3 grams per serving
Icings or glazes used on baked goods (cookies, pastries, brownies, and angel food, chiffon and pound cakes)	30 percent
Light ice cream (ice milk), frozen milk dessert, low-fat and non-fat frozen yogurt and related frozen novelties	3 percent
Low fat, reduced fat, diet, energy or nutrient fortified bars	10 percent
Regular and dietetic hard candies	15 percent
Dietetic soft candies	10 percent
Powdered products prepared with milk	5 grams per serving

Arla cites studies investigating the absorption, distribution, metabolism and excretion of ingested D-tagatose. Arla's GRAS notice describes published and unpublished studies in rats and pigs demonstrating that approximately 20-30 percent of ingested D-tagatose is absorbed from the small intestine, and the remaining unabsorbed D-tagatose undergoes microbial fermentation to short chain fatty acids, carbon dioxide, methane and hydrogen gas. Additional published studies indicate that the absorption of D-tagatose is passive and noncompetitive with the carrier-mediated facilitated diffusion uptake of fructose. The first step in the metabolic pathway for

[1]As we discussed with you by telephone on July 24, 2001, and in a meeting on August 3, 2001, FDA does not concur with the normalization methodology used by Arla to estimate the dietary intake of D-tagatose. However, FDA's own estimate of the dietary intake for D-tagatose under the intended conditions of use (i.e., 7.5 g/p/d at the mean and 15 g/p/d at the 90th percentile) is similar to Arla's estimate.

absorbed D-tagatose is phosphorylation to D-tagatose-1-phosphate by the enzyme fructokinase (now known as ketohexokinase). This intermediate is then split by the enzyme aldolase B to D-glyceraldehyde and dihydroxyacetone phosphate (now known as glycerone phosphate). Although absorbed fructose is metabolized via this same metabolic pathway, the fructose intermediate (D-fructose-1-phosphate) is cleaved by aldolase B at approximately twice the rate of the tagatose intermediate (D-tagatose-1-phosphate), as a consequence of a higher affinity of the enzyme for the fructose intermediate.

Arla's GRAS notice describes published and unpublished genetic toxicity studies, developmental toxicity studies and acute and subchronic feeding studies conducted with D-tagatose. From these studies, Arla concludes that dietary exposure to D-tagatose did not result in any genetic or developmental toxicity or teratogenic effects. The only notable treatment-related effects were seen in Sprague Dawley rats administered D-tagatose in the diet for 90 days. In this study, increased liver weights were observed in Sprague Dawley rats administered D-tagatose at 10-20 percent in the diet and hepatocellular hypertrophy was observed in Sprague Dawley rats administered D-tagatose at 15-20 percent in the diet. These effects were not associated with any adverse clinical symptoms or histopathological evidence of overt hepatotoxicity. The no observed adverse effect level (NOAEL) for D-tagatose determined from this study was 5 percent of the diet (i.e., 2.3 - 6.7 g/kg body weight /day). Other feeding studies, in Wistar rats fed D-tagatose at 10 percent of the diet for six months or in pigs fed D-tagatose at 20 percent of the diet for 33 days, showed no liver enlargement.

Arla's GRAS notice describes a published clinical trial to study potential effects of D-tagatose on the volume of the human liver and postprandial liver glycogen concentration in healthy male subjects. No significant differences in clinical chemistry including plasma uric acid levels, hematological parameters, or urinary endpoints were noted between subjects fed D-tagatose or sucrose. Liver volumes increased significantly over time with both treatments. However, there was no difference between individuals given D-tagatose and those given sucrose. Post-prandial liver glycogen concentrations after the prolonged consumption of D-tagatose or sucrose did not differ significantly from those recorded during pretreatment.

Arla's GRAS notice describes published single-dose and repeated-dose studies in healthy or diabetic human subjects. The predominant effects associated with excessive consumption were gastrointestinal disturbances attributed to osmotic effects from incompletely absorbed D-tagatose. At doses of up to 25 g D-tagatose per meal, flatulence was generally the only side effect, with nausea, borborygmi (i.e. rumbling or gurgling noises in the gut), colic and laxation noted at higher doses. Such effects are also commonly associated with excessive consumption of other poorly digestible sugars and polyols.

In its original submission and in an amendment dated September 19, 2001, Arla addresses the potential for D-tagatose ingestion to increase plasma concentrations of uric acid. The presence of chronically elevated plasma uric acid levels (i.e., hyperuricemia) is one known risk factor for the development of gout, which is a group of disorders of purine metabolism. Arla cites published reports describing a possible mechanism by which phosphorylation of D-fructose or D-tagatose could lead to increased degradation of purine nucleotides, increased release of uric acid from the liver and, thus, hyperuricemia. Arla also provides background on the known causes of

asymptomatic hyperuricemia, which are unrelated to the mechanism that is hypothesized to be involved in the increase in serum uric acid levels following ingestion of D-tagatose.

In its original submission and its amendment, Arla presents its safety assessment of the potential for D-tagatose ingestion to induce hyperuricemia. In this assessment, Arla describes the findings from human consumption and tolerance studies with D-tagatose, fructose, or sucrose, specifically as they relate to effects on uric acid metabolism. Arla addresses the following issues: 1) the potential for D-tagatose ingestion to increase serum uric acid levels in healthy and diabetic persons under the conditions of intended use; 2) the potential for D-tagatose ingestion to increase serum uric acid levels in individuals with asymptomatic hyperuricemia; 3) the potential uricemic response in individuals with symptomatic gouty disease; 4) the potential for co-ingestion of D-tagatose and fructose to result in a supra-additive or synergistic uricemic effect; and 5) the potential for chronic ingestion of D-tagatose to lead to increased intestinal absorption and consequently to increased serum uric acid levels over time. Based on its review of these issues, Arla concludes that there exists no reason to expect a postprandial increase of plasma uric acid concentrations in response to the ingestion of single 15-g doses of D-tagatose in healthy, diabetic, hyperuricemic or gouty individuals. Arla also concludes that there are no cumulative effects on fasting serum uric acid levels after chronic intake of D-tagatose (i.e., 75 g/day for eight weeks, or 45 g/day for 12 months). Overall, Arla concludes that the available data support a determination that the estimated dietary intake of D-tagatose under intended conditions of use (i.e., 6.6 g/p/d at the mean and 14.9 g/p/d at the 90th percentile) presents no risk to human health as a consequence of the potential for D-tagatose to induce hyperuricemia.

Based on the information provided by Arla, as well as other information available to FDA, the agency has no questions at this time regarding Arla's conclusion that D-tagatose is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of D-tagatose. As always, it is the continuing responsibility of Arla Foods Ingredients amba to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FFDCA), a food is misbranded if its labeling is false or misleading in any particular. Section 403(r) of the FFDCA lays out the statutory framework for a health claim. In describing the intended use of D-tagatose and in describing the information that Arla relies on to conclude that D-tagatose is GRAS under the conditions of its intended use, Arla raises an issue under these labeling provisions of the FFDCA. This issue consists of physiological effects of D-tagatose that Arla views as "beneficial" - e.g, whether D-tagatose is non-cariogenic or exerts a "prebiotic" effect. This issue is the purview of the Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS) in the Center for Food Safety and Applied Nutrition (CFSAN). The Office of Food Additive Safety (OFAS) neither consulted with ONPLDS on these labeling issues nor evaluated the information in your notice to determine whether it would support any claims made about D-tagatose on the label or in labeling.

In the notice, Arla states its intention to use D-tagatose in several food categories, including foods for which standards of identity exist, located in 21 CFR. FDA notes that an ingredient that is lawfully added to food products may be used in a standardized food only if permitted by the

applicable standard of identity. If you have any questions about the use of D-tagatose in standardized foods that would be marketed in the United States, you should contact the staff in the Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling, and Dietary Supplements, HFS-820, 200 C Street S.W., Washington, DC 20204. You can reach this Division by telephone at (202)205-4168.

In the notice, Arla states its intention to use D-tagatose in "light," "low calorie," "sugar free," "sugarless," "low fat" and "reduced fat" food products. FDA notes that the use of these terms are nutrient content claims, defined by regulation, that must be used in accordance with 21 CFR 101.13 and the relevant specific nutrient content claim regulations in 21 CFR Part 101. In addition, when foods governed by a standard of identity are modified to make an expressed nutrient content claim defined by regulation, these foods are subject to and must be in compliance with regulations contained in 21 CFR 130.10. If you have any questions about nutrient content claims, OFAS suggests that you contact the Division of Standards and Labeling Regulations at the address or telephone number given above.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in your notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,

Laura M Tarantino / for

Alan M. Rulis, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition